

=> b casre
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FILE CONTENT:1840 - 9 Mar 2008 VOL 148 ISS 11

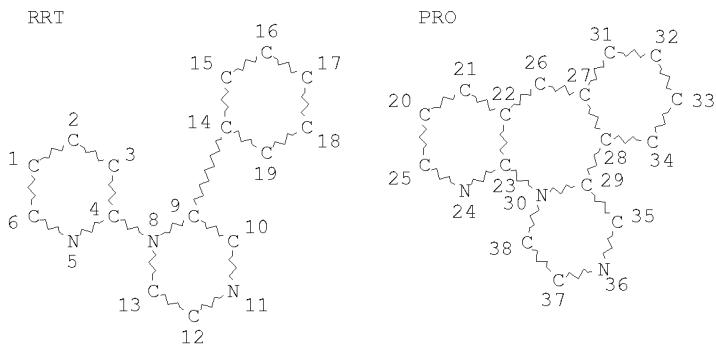
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* *
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* *****

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que sta 18
L6 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 37

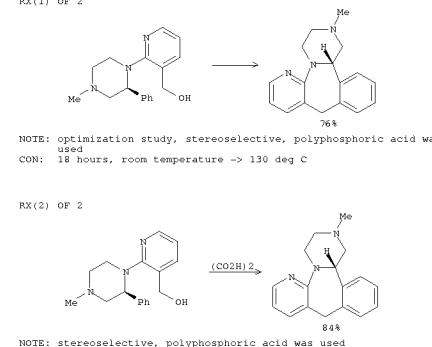
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100.0% DONE 30 VERIFIED 30 HIT RXNS 13 DOCS
SEARCH TIME: 00.00.01

=> d bib abs crd 113 tot

AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-4-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in *N*-methylpyrrolidinone and polyphosphoric acid was added. The title compound was obtained in 68% yield with 99.2% ee.

L13 ANSWER 1 OF 1 CASREACT COPYRIGHT 2008 ACS on STN (Continued)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN END-OF-REPORT.

10 / 564193

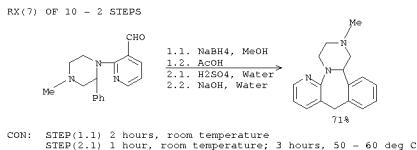
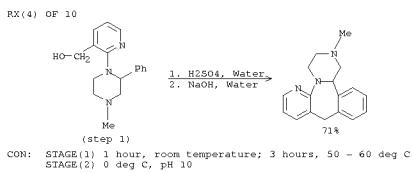
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L14 ANSWER 1 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
 AN 143:7729 CASREACT
 TI Preparation of mirtazapine antidepressant
 IN Yang, Yushe; Guo, Baishu; Chen, Kaixian; Ji, Ruyun
 PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China
 SO Faming Zhanli Shengqing Gongkai Shuomingshu, 9 pp.

CODEN: CNXXEV
 DT Patent
 LA Chinese
 FAN,ET AL.

PATENT NO. KIND DATE APPLICATION NO. DATE
 PI CN1012429813 A 20011229 2001CN-000145561 20011229
 PRAI 1001CN000145561 A 20011229

AB The method comprises substituting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanoypyridine in DMF or DMSO to obtain 2-(3-cyano-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with Raney Ni/NaH2PO2 in water-acetic acid-pyridine mixed solvent at 50-60° to obtain 2-(3-formyl-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with NaBH4 or Zn/H4 in alc. at room temperature, cyclizing with concentrated H2SO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.

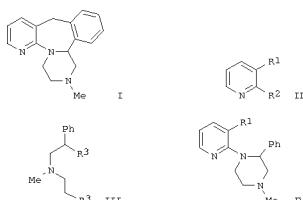


L14 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
 AN 138:304301 CASREACT
 TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
 IN Slinger, Claude; Liberman, Anita; Finkelstein, Nina
 PA English
 SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
 CODEN: USXXCO
 DT Patent
 LA English
 FAN,ET AL.

PATENT NO. KIND DATE APPLICATION NO. DATE

PI US--2003069417 A1 20030410 2002US-000206344 20020729
 CN----1679586 A 20051012 2005CN-010004288 200504118
 CN----1679587 A 20051012 2005CN-010004289 200504118
 CN----680365 A 20051012 2005CN-010004290 200504118
 US--2003051718 A1 20031233 2001US-000900646 20010706
 US--6545149 B2 20030408
 US--2003080094 A1 20030508 2002US-000283093 20021030
 US--2003080095 A1 20030508 2002US-000283094 20021030
 US--2003120068 A1 20030626 2003US-000348757 200303123
 US--2003135943 A1 20030737 2003US-000368441 200303220
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 US--2005201117 A1 2005050407 2005AU-000201117 20050315

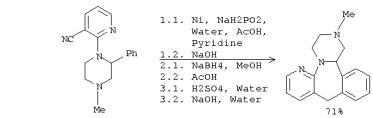
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 2000AU-00043577 200004128
 2000CN-000807574 200004128
 2001US-000283093 20010706
 2003US-000283093 20031030
 2003US-000368441 20030220
 OS MARPAT 138:304301
 GI



AB Mirtazapine (I) was prepared by reacting substituted pyridine II (R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2) with compound III (R3 = Cl, F, Br, I) followed by treating the resulting piperazine IV with ring closing. Reactants IV and V, and products VI and VII (R1 = CH2CO2H) may be prepared by hydrolyzing IV (R1 = CHI with KOH at a temperature of at least about 140°C. New processes for recrystn. of I form crude mirtazapine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.5% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.

L14 ANSWER 1 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

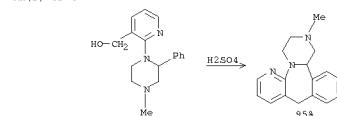
RX(9) OF 10 - 3 STEPS



RX(3) OF 4

L14 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

RX(3) OF 4

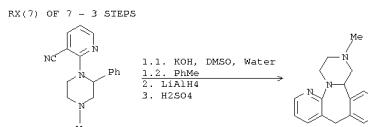


L14 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
 AN 137:216962 CASREACT
 TI Methods for the preparation of mirtazapine intermediates
 IN Matzger, Leonid; Witzel, Shlomit
 PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
 SO PCT Int. Appl., 12 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 PAN, CNT

PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO-2002070513 A1 20020912 2002WO-US0004340 20020214
 WO-2002070513 A1 20020912 2002WO-US0004340 20020214
 W: AE, AG, AL, AM, AI, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MM, MX, MZ, NO, NZ, OM, PH, RS, RO, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, VN, ZA, ZW
 RW: GH, GM, KE, LS, MM, MS, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG
 CA-243846 A1 20020214 2002CA-00243846 20020214
 AU-2002077320 A1 20020214 2002AU-000247120 20020214
 US-2002165238 A1 20021107 2002US-000073960 20020214
 US-6774230 B1 20040810
 EP-1370549 A1 20031217 2002EP-000714893 20020214
 R: AT, BE, CH, DE, DU, ES, FR, GB, GR, IE, IT, LU, NL, SE, MC, PT, SE, TR, TZ, UA, UG, US, VN, ZA, ZW, ZR, ZW
 JP-2005105108 A1 20050120 2005JP-000569833 20020214
 IN-2003IN00777 A 20050429 2003IN-MN00000777 20030822

PRAI 2001US-00272699P 20010301
 2002WO-US0004340 20020214
 AB The preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydro (1) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-cyan-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.

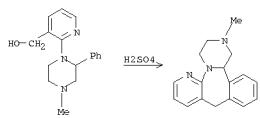
L14 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)



NOTE: 2) no exptl., 3) no exptl.

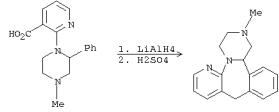
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(4) OF 7



NOTE: no exptl.

RX(6) OF 7 - 2 STEPS



NOTE: 1) no exptl., 2) no exptl.

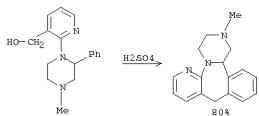
L14 ANSWER 4 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

AN 136:401782 CASREACT
 TI Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
 IN Matsuda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
 PA Sumitomo Fine Chemicals Co., Ltd., Japan
 SO Eur. Pat. Appl., 10 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 PAN, CNT

PATENT NO. KIND DATE APPLICATION NO. DATE
 PI EP-1209159 A2 20020529 2001EP-00011102 20010508
 EP-1209159 A3 20030305
 EP-1209159 A1 20040117
 R: AT, BE, CH, DE, DU, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MR, CY, AL, TR
 US-200205413 A1 20020530 2001US-000842871 20010427
 AU-20031209 A1 20030616 2001AU-000040301 20010430
 AU-781974 B2 20050623
 CA-2346195 A1 20020527 2001CA-002346195 20010502
 AT-282616 T 20041215 2001AT-00011102 20010508
 PT-1209159 T 20050131 2001PT-00011102 20010508
 EG-1209159 T 20050516 2001EG-00011102 20010508
 JP-2002220390 A 20020809 2001JP-000291663 20010925

PRAI 2000JP-000359891 20001127
 AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual water and having a large particle diameter of from 10-50 μ m, are described. Where: one filters a lower alc. alc. methanol solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.

RX(1) OF 1



L14 ANSWER 5 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

AN 136:369741 CASREACT
 TI A novel method for preparation of piperazine and its derivatives
 IN Sebastian, Sonny; Patel, Metal Virendra; Thennatti, Rajamannar
 PA Sanku Pharmaceutical Industries Ltd., India
 SO PCT Int. Appl., 23 pp.
 CODEN: PIXXD2

DT Patent
 LA English
 PAN, CNT

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO-2002038552 A1 20020516 2001WO-IN0000123 20010629
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 RW: GH, GM, KE, LS, MM, SD, GL, ES, TZ, UC, SW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, IG
 IN-190478 A2 20020802 2000IN-MU0000994 20001107
 AU-2001078669 A 20020521 2001AU-000078669 20010629
 BE-1013317 A6 20010106 2001BE-000000513 20010727
 CR-1014242 A6 20010515 2001CH-000001424 20010802
 US-2002050538 A1 20020318 2001US-000037303 20011025
 US-6603003 B2 20030805 2001IN-MU0000411 20020506

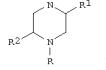
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2000IN-MU0000994 20001107

2001MO-IN0000129 20010629

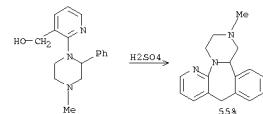
MARPA/136:369741

GI

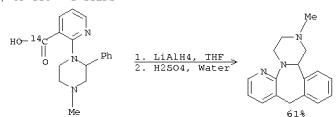


AB Compds. I [R = H, -CH2-alkyl, phenyl-CH2-alkyl; R1 = H, Me, (unsubstituted phenyl); R2 = H, Me, fluoromethyl] useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting RiCOOC2R with H2NC2H2NR2HNR to give 3,4-dehydropiperazine-2-one and its derivs., followed by reacting with a reducing agent to yield I. Thus, 1-(α -methyl-3-phenylpiperazine was prepared and used as starting material for preparation of 1,2,3,4,10,14b-hexahydro- α -methyl-pyrazinoc[2,1-d]pyridine.

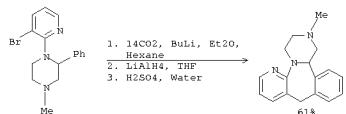
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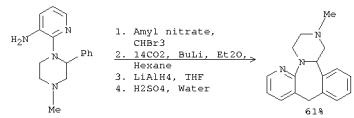
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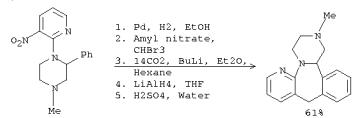
RX(54) OF 118 - 3 STEPS



RX(55) OF 118 - 4 STEPS



RX(99) OF 118 - 5 STEPS



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DICTIONARY FILE UPDATES: 10 MAR 2008 HIGHEST RN 1007341-18-5

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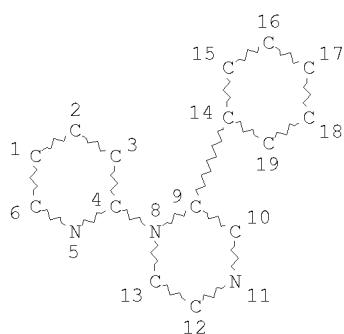
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<http://www.cas.org/support/stngen/stndoc/properties.html>

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L15 STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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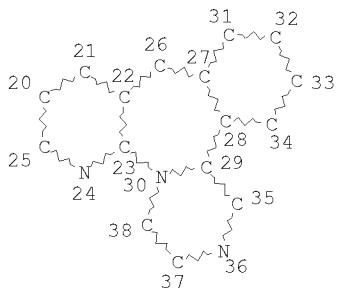
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NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

L17 34 SEA FILE=REGISTRY SSS FUL L15

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SEARCH TIME: 00.00.01

=> d que sta 120
L18 STR



NODE ATTRIBUTES:

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 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE

L20 131 SEA FILE=REGISTRY SSS FUL L18

100.0% PROCESSED 100374 ITERATIONS
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131 ANSWERS

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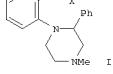
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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126 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 AC5 ON SIN
AN 2005;55224 HCAPLUS
DN 142134623
TI Preparation of enantiomerically pure (S)-mirtazapine
IN (S)-mirtazapine; Hubertus; Van De Ven, Adrianus Antonius Martinus;
Kempton, Gerardus Johannes
PA Akzo Nobel N.V., Neth.
SO PCT Int. Appl. 16 pp.
CODEN PIXXD2

GI



AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in *N*-methylpyrrolidinone and polyphosphoric acid was added. The title compound was isolated in 68% yield with 99.2% ee.

IT 61327-87-9, (S)-Mirtazapine
 RL: IMP (Industrial manufacturer); SPN (Synthetic
 Preparation name)
 (asym.) synthesis of (S)-mirtazapine via acid-induced cyclization of

$$(S)-1-(3-(hydroxymethyl)-2-pyridyl)-4-methyl-2-phenylpiperazine$$

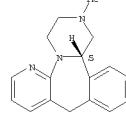
IT 824954-89-4 824954-90-7
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (asym.) synthesis of mirtazapine via acid-induced cyclization of

$$(S)-1-(3-(hydroxymethyl)-2-pyridyl)-4-methyl-2-phenylpiperazine$$

IT 61327-88-9, (S)-Mirtazapine
 RL: IMP (Industrial manufacturer); SPN (Synthetic
 Preparation name)
 (asym.) synthesis of (S)-mirtazapine via acid-induced cyclization of

$$(S)-1-(3-(hydroxymethyl)-2-pyridyl)-4-methyl-2-phenylpiperazine$$

126 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS ON STN (Continued)
 RL: RCT (Reactant); RACT (Reactant or reagent);
 PREP (Preparation)
 (asym. synthesis of (S)-mirtazapine via acid-induced cyclization of
 (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)
 RN 61337-87-9 HCAPLUS
 CN Pyrazin[2,1-a]pyrrolidine[2,3-c][2]benzepazine, 1,2,3,4,10,14b-hexahydro-2-
 methyl-, (4R)- (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10 / 564193

=> d bib abs hitstr 128 tot

L28 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:460192 HCAPLUS

DN 143:132393

TI Preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine

IN Li, Yusheng; Xu, Jianyan; Shi, Huili

PA Shanghai Institute of Pharmaceutical Industry, Peop. Rep. China

SO Faming Zhanli Shengqing Gongkai Shuomingshu, No. pp. given

CODEN: CNXEV

DT Patent

LA Chinese

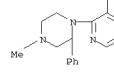
PAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PT CN 61338-13-4 2003CN-000115386 200303213 <--

L28 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

PTA1 2003CN-000115386 200303213 <--



● K

OS CASREACT 143:132393

AB The title compound (I), an intermediate for the antidepressant mirtazapine, is prepared by reduction of 1-(3-carboxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine (II) with diborane in ethers. Thus, reduction of II with NaBH4 and HCl in ethyl acetate gave I in 89% yield at 60° for 2 h gave 89% I.

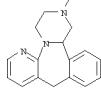
IT 85650-52-8 HCAPLUS

RU: PNU (Preparation, unclassified); PREP (Preparation) (preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)

RN 85650-52-8 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-

methyl- (CA INDEX NAME)



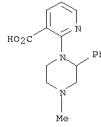
IT 61338-13-4 2003CN-000115386-1

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)

RN 61338-13-4 HCAPLUS

CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 34330-55-1 HCAPLUS

CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, potassium salt (SCI) (CA INDEX NAME)

L28 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN

AN 2005:436399 HCAPLUS

DN 143:7728

TI Preparation of mirtazapine antidepressant

IN Li, Yusheng; Guo, Baishu; Chen, Kaijian; Ji, Ruyun

PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China

SO Faming Zhanli Shengqing Gongkai Shuomingshu, 9 pp.

CODEN: CNXEV

DT Patent

LA Chinese

PAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

PT CN 61337-89-0 2001CN-000145561 20011229 <--

PTA1 2001CN-000145561 20011229 <--

OS CASREACT 143:7729

AB The method comprises substituting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyano pyridine in DMS or DMSO to obtain 2-(3-cyano-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with NaBH4 or Ni(NH3)6Cl2 in water at 0-60°, then cyclizing with H2SO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.

IT 85650-52-8 HCAPLUS

RU: RCT (Reactant); RACT (Reactant or reagent); PREP (Preparation); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);

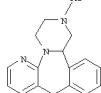
PREP (Preparation); USES (Uses)

(preparation of mirtazapine antidepressant)

RN 85650-52-8 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-

methyl- (CA INDEX NAME)



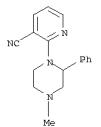
IT 61337-89-0P 61337-89-1P 8565234-23-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of mirtazapine antidepressant)

RN 61337-89-0 HCAPLUS

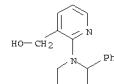
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61337-89-1 HCAPLUS

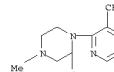
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



RN 856524-23-3 HCAPLUS

CN 3-Pyridinecarboxaldehyde, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



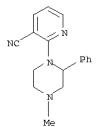
IT 61337-89-0P 61337-89-1P 8565234-23-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

(preparation of mirtazapine antidepressant)

RN 61337-89-0 HCAPLUS

CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61337-89-1 HCAPLUS

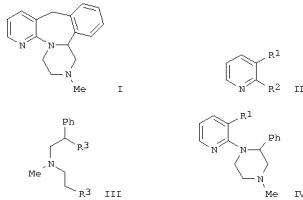
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 3 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN
 AN 2003:282146 HCPLUS
 DN 138:304301
 TI New synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
 IN Singer, Claude; Liberman, Anita; Finkenstein, Nina
 PA Israel
 SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
 CODEN: USXXCO
 DP Patent
 LA English
 FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US---2003049417	A1	20030410	2002US-000266344	200202729 <--
CN---1679586	A	20051012	2005CN-010004288	20000418 <--
CN---1680374	A	20051012	2005CN-010004289	20000418 <--
CN---1680365	A	20051012	2005CN-010004290	20000418 <--
US---2001051718	A1	20011213	2001US-000900646	20010706 <--
US---200304849	B2	20030608		
US---2003048094	A1	20030508	2002US-000282093	20021030 <--
US---6576764	B2	20030610		
US---2003120068	A1	20030622	2003US-000248757	20030123 <--
US---2003135943	A1	20030717	2003US-000368441	20030220 <--
US---20040414591	A1	20040509	2004US-000800918	20040316 <--
AN---2003120137	A1	20030407	2005AU-000201117	20050315 <--

PRAT 1999US-00130047P P 19990419 <--
 2000US-00182745P P 20000218 <--
 2000US-000552485 P 20000418 <--
 2000US-000552487 A2 20000418 <--
 2000US-000552488 A2 20000418 <--
 2000US-000807574 A3 20000418 <--
 2001US-000900646 A3 20010706 <--
 2002US-000282093 A3 20021030 <--
 2003US-000368441 B1 20030220 <--

OS CASREACT 138:304301; MARPAT 138:304301
 GI



AB Mirtazapine (I) was prepared by reacting substituted pyridine II (R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2) with compound III (R3 = Cl, F, Br, I) followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CO2H) may be prepared by hydrolyzing IV (R1 = CN with KOH at a temperature of at least about 140°C. New processes for the cyclization of 4-formyl-1-(4-methyl-2-phenyl-1-piperazinyl)-2-pyridine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.5% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.

IT 341512-90-1P

L28 ANSWER 3 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses);
 TI Preparation and crystallization of mirtazapine water adduct
 IN Singer, Claude; Liberman, Anita; Finkenstein, Nina
 PA Israel
 SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
 CODEN: USXXCO
 DP Patent
 LA English
 FAN.CNT 2

RN 341512-90-1 HCPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, hydrate (9CI) (CA INDEX NAME)

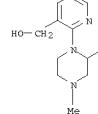


● 2 H2O

IT 61327-89-1P 61328-13-4P
 RL: IMP (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent);
 TI Preparation and crystallization of piperazine ring-containing compds. such as mirtazapine
 IN Singer, Claude; Liberman, Anita; Finkenstein, Nina
 PA Israel
 SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
 CODEN: USXXCO
 DP Patent
 LA English
 FAN.CNT 2

RN 61327-89-1 HCPLUS

CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

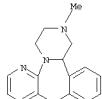


RN 61328-13-4 HCPLUS
 CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



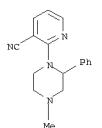
IT 85650-52-8P, Mirtazapine
 RL: IMP (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
 PREP (Preparation); USES (Uses);
 TI Preparation and crystallization of piperazine ring-containing compds. such as

L28 ANSWER 3 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)
 RN 85650-52-8 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61327-88-0
 RL: RCT (Reactant); RACT (Reactant or reagent);
 TI Preparation and crystallization of piperazine ring-containing compds. such as mirtazapine
 IN 61327-88-0 HCPLUS

CN 3-Pyridinecarboxonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



L28 ANSWER 4 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN

AN 2002:695977 HCPLUS
 DN 137:216962
 TI Methods for the preparation of mirtazapine intermediates
 IN Metzger, Leonid; Wizel, Shlomit
 PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SO ECT Int. Appl., 12 PP.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 2

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO---2002070513 A1 20020919 2002WO-US0004340 20020214 <--

WO---2002070513 A9 20021101 <--

W: AE, AG, AL, AJ, AU, AZ, BA, BS, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DU, DN, DZ, EC, EE, ES, FI, GR, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KE, LC, LK, LR, LS, LT, LU, LV, MA, ME, MG, MR, MM, MW, MX, MZ, NO, NE, OM, PH, PT, PR, PS, SI, SV, TR, TW, TZ, UA, UG, US, UZ, VN, YA, ZA, ZM, ZW
 RM: GH, GM, KE, LS, MW, ME, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BE, BJ, CF, CG, CI, CR, GA, GN, GO, GM, MR, NE, SN, TD, TG, CA---328442 A1 200209214 2002WO-US0024316 20020214 <--

AU---2002247130 A1 20020919 2002AU-000347120 20020214 <--

US---2002165238 A2 20021107 2002US-000073940 20020214 <--

US---6774230 B2 20040810 <--

EP---1370549 A1 20031217 2002EP-000714893 20020214 <--

R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, SE, MC, PT, SI, LT, MT, PL, FI, RO, CY, PT, TR, TW, TZ, UG, ZA, ZW
 JP---2005501808 T 20050120 2002JP-000569833 20020214 <--

IN-2002MN000777 A 20050429 2002IN-MN0000777 20030822 <--

PRAI 2001US-00272699P P 20010301 <--

2002US-000736420 W 20020214 <--

OS CASREACT 137:216962

AB The preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate (I) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.

II 457601-25-1B, 1-(3-Carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate
 RL: IMP (Industrial manufacture); RCT (Reactant or reagent);
 SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent);
 TI Preparation of 1-(3-Carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine

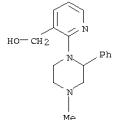
RN 457601-25-1B, 1-(3-Carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate
 CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, dihydrate (9CI) (CA INDEX NAME)



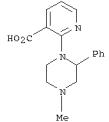
● 2 H2O

IT 61327-89-1P, 1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation);
 THU (Therapeutic use); BIOL (Biological study); PREP (Preparation);
 USES (Uses);
 TI Preparation and crystallization of 1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine

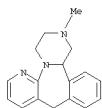
L28 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
 RN 61337-89-1 HCAPLUS
 CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61338-13-4 HCAPLUS
 CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

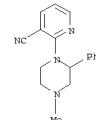


IT 85650-52-8P, Mirtazapine
 RL: IMP (Industrial manufacture); SPP (Synthetic preparation); PREP (Preparation)
 (preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine
 dihydrochloride intermediate for mirtazapine)
 RN 85650-52-8 HCAPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-88-0, 1-(3-Cyano-2-pyridyl)-4-methyl-2-phenylpiperazine
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine
 dihydrate as intermediate for mirtazapine)
 RN 61337-88-0 HCAPLUS
 CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
 AN 2002:406942 HCAPLUS
 DN 136:401782

TI Process for the manufacture of anhydrous, solvent-free mirtazapine

IN Masuda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi

PA Sumika Fine Chemicals Co., Ltd., Japan

SO Eur. Pat. Appl., 10 pp.

CODEN: EPXXDW

DT Patent

LA English

CN 1

PATENT NO. KIND DATE APPLICATION NO. DATE
 PI ----- A1 20020529 2001EP-000111102 20010508 <--
 EP----- A2 20030305 2001EP-000111102 20010508 <--
 EP----- B3 20041117 2001EP-000111102 20010508 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, IR
 US--2002065413 A1 20020530 2001US-000642871 20010427 <--
 US--2002065420 B2 20020530 2001US-000642871 20010427 <--
 AU--2001040301 A 20020606 2001AU-000040301 20010430 <--
 AU-----781974 B2 20050623 2001AU-000040301 20010430 <--
 CA----2346195 A1 20020527 2001CA-002346195 20010502 <--
 AT-----282616 I 20041211 2001AT-000111102 20010508 <--
 PT-----282616 T 20041211 2001PT-000111102 20010508 <--
 ES-----2321340 T3 20050516 2001ES-000011102 20010508 <--
 JP--2002220390 A 20020801 2001JP-000291863 20010925 <--
 PPAI 2000JP-000359891 A 20001127 <--

OS CASREACT 136:401782

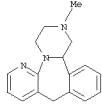
AB Method for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μ m, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.

IT 85650-52-8P, Mirtazapine
 RL: IMP (Industrial manufacture); DEP (Physical, engineering or chemical process); PRO (Properties); PUR (Purification or recovery); PIP (Physical process); PREP (Preparation); PROC (Process)

(process for the manufacture of anhydrous solvent-free mirtazapine crystals)

RN 85650-52-8 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-89-1
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (process for the manufacture of anhydrous solvent-free mirtazapine crystals)

RN 61337-89-1 HCAPLUS

CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

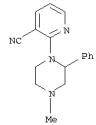
L28 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
 AN 2002:369741 HCAPLUS
 DN 136:369741
 TI A process for preparation of piperazine and its derivatives
 IN Sebastian, Sonny; Patel, Rakesh Virendra; Thenmann, Rajamannar
 PA Sun Pharmaceutical Industries Ltd., India
 SO PCT Int. Appl., 23 pp.
 CODEN PIXXD2
 DT Patent
 LA English
 FN, CNT

PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO-2002038552 A1 20020516 2001WO-IN0000129 20010629 <-
 W: AE, AG, AL, AM, AU, BE, BR, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DS, BE, ES, FI, GB, GD, GR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LU, LV, LU, MA, MD, MG, MK, MN, MW, MX, ME, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, IM, TR, TZ, UA, UG, US, UZ, ZA, ZW
 RW: GH, GM, IS, LS, MW, ME, SD, SL, SZ, TZ, UG, SW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IL, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 IN-190478 A1 20030802 2000IN-MU0000994 20001107 <-
 AU-2001070699 A 20020516 2001AU-00007609 20010705 <-
 BE-2001023217 A6 20010606 2001BE-000000513 20010727 <-
 CH-692342 A5 20020515 2001CH-000001428 20010802 <-
 US-2002095038 A1 20020718 2001US-000037309 20011025 <-
 US-6603003 B2 20030805 2001US-000037309
 IN-2000IN-IN0000994 A 20040408 2002IN-MU0000411 20020506 <-
 PRAI 2001IN-IN0000129 M 20010629 <-
 OS CASREACT 136:369741; MARPAT 136:369741
 GI



AB Compds. I (R = H, C1-6 alkyl, phenyl-CH₂-alkyl; R1 = H, Me, (un)substituted phenyl; R2 = H, Me, fluoromethyl) useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting RICOCOR with H2NCH2CHR2NHR to give 3,4-dihydropiperazine-2-one and its 1,2-dihydro form, followed by reduction with LiAlD₄ to give the yield. Thus, 3-methyl-3-aminopyridine was prepared and used as starting material for preparation of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c]1,2,3,4,10,14b-hexahydropyrazine. R: Me, R1: Ph, R2: H, R3: Me, R4: H, R5: Me, R6: H, R7: H, R8: H, R9: H, R10: H, R11: H, R12: H, R13: H, R14: H, R15: H, R16: H, R17: H, R18: H, R19: H, R20: H, R21: H, R22: H, R23: H, R24: H, R25: H, R26: H, R27: H, R28: H, R29: H, R30: H, R31: H, R32: H, R33: H, R34: H, R35: H, R36: H, R37: H, R38: H, R39: H, R40: H, R41: H, R42: H, R43: H, R44: H, R45: H, R46: H, R47: H, R48: H, R49: H, R50: H, R51: H, R52: H, R53: H, R54: H, R55: H, R56: H, R57: H, R58: H, R59: H, R60: H, R61: H, R62: H, R63: H, R64: H, R65: H, R66: H, R67: H, R68: H, R69: H, R70: H, R71: H, R72: H, R73: H, R74: H, R75: H, R76: H, R77: H, R78: H, R79: H, R80: H, R81: H, R82: H, R83: H, R84: H, R85: H, R86: H, R87: H, R88: H, R89: H, R90: H, R91: H, R92: H, R93: H, R94: H, R95: H, R96: H, R97: H, R98: H, R99: H, R100: H, R101: H, R102: H, R103: H, R104: H, R105: H, R106: H, R107: H, R108: H, R109: H, R110: H, R111: H, R112: H, R113: H, R114: H, R115: H, R116: H, R117: H, R118: H, R119: H, R120: H, R121: H, R122: H, 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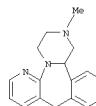
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CMF C2 H2 O4RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L28 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)					
AN 2001:396868 HCAPLUS					
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TI Anhydrous mirtazapine crystals and process for the production thereof					
IN Iishi, Etsushi; Manabe, Yoshiyuki PA Sumika Fine Chemicals Co., Ltd., Japan SO PCT Int. Appl., 37 PP. CODEN: PIXXD2					
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2000WO-JP0004835	W	20000719			
2000WO-JP0006687	W	20000928			
AB This document discloses: lowly hygroscopic anhydrous mirtazapine crystals exhibiting a moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h; a process for producing anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h characterized by drying crystals of mirtazapine hydrate; and a process for producing crystals of mirtazapine hydrate characterized by crystallizing crude mirtazapine by using a water soluble polar organic solvent and water. By using this production method, stable anhydrous mirtazapine having little hygroscopicity can be produced by a convenient industrial method. The anhydrous mirtazapine crystals are suitable as active ingredients in an antidepressant.					
IT 343512-89-8P 343512-90-1P					
PL: PEP (Physical, engineering or chemical process); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation); PROC (Process); Process)					
RN 343512-89-8 HCAPLUS					
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, hydrate (2:1) (CA INDEX NAME)					



●1/2 H2O

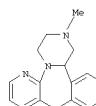
RN 343512-90-1 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-L28 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
methyl-, hydrate (9CI) (CA INDEX NAME)

●R H2O

IT 85650-52-0P, Mirtazapine
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
PREP (Preparation); USES (Uses);
(anhydrous mirtazapine crystals and process for production thereof)

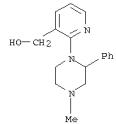
RN 85650-52-8 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

IT 61337-89-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(anhydrous mirtazapine crystals and process for production thereof)

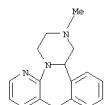
RN 61337-89-1 HCAPLUS

CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

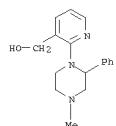
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)					
AN 2001:396868 HCAPLUS					
DN 135:12413					
TI Anhydrous mirtazapine crystals and process for producing the same					
IN Iishi, Etsushi; Manabe, Yoshiyuki PA Sumika Fine Chemicals Co., Ltd., Japan SO PCT Int. Appl., 37 PP. CODEN: PIXXD2					
DT Patents					
LA Japanese					
PAN.CNT 2					
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO-2001038329	A1	20010531	2000WO-JP0004835	20000719	<--
W: AU, CA, IN, JP, US RM: AU, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU-2000060199	A	20010604	2000AU-000060199	20000928	<--
CA-2370376	C	20010531	2000CA-002370376	20000928	<--
CA-2370376	A1	20010531			
WO-2001038330	A1	20010531	2000WO-JP0006687	20000928	<--
W: AU, CA, IN, JP, US RM: AU, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU-2000061471	A	20010604	2000AU-000074471	20000928	<--
AU-2000061471	B2	20030724	2000EP-000962908	20000928	<--
EP-1225174	A1	20020724	2000EP-000962908	20000928	<--
EP-1225174	B1	20040317			
R: AU, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, NL, SE, MC, PT, IE, FI, CY					
AT-261966	T	20040415	2000AT-000962908	20000928	<--
PT-1225174	T	20040531	2000PT-000962908	20000928	<--
ES-2214318	T3	20040916	2000ES-000962908	20000928	<--
JP-3699680	B2	20050928	2001JP-000540093	20000928	<--
US-2002103372	A1	20020801	2002US-000041495	20020110	<--
US-2002103372	A1	20030710	2003US-000337277	20030107	<--
US-6723845	B2	20040420			
US-2004138447	A1	20040715	2003US-000743740	20031224	<--
US-7297790	A	20071120			
PRA1 13959D-000613349	A	13959000			
2000JP-000613349	W	20000310			
2000WO-JP0004835	W	20000719			
2000WO-JP0006687	W	20000928			
2000US-0000697329	A2	20001027			
2002US-000041495	A2	20020110			
2002US-000033727	A2	20030717			
AB This document discloses: lowly-hygroscopic anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h; a process for producing anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h characterized by drying crystals of mirtazapine hydrate; and a process for producing crystals of mirtazapine hydrate characterized by crystallizing crude mirtazapine by using a water soluble polar organic solvent and water. By using this production method, stable anhydrous mirtazapine having little hygroscopicity can be produced by a convenient industrial method. The anhydrous mirtazapine crystals are usable as active ingredients in an antidepressant.					
85650-52-0P, Mirtazapine					
PL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses); (preparation of anhydrous mirtazapine crystals)					
RN 85650-52-8 HCAPLUS					
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)					

128 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

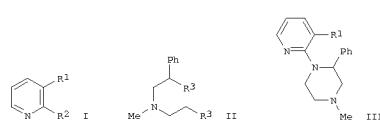


IT 61337-89-1
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of anhydrous mirtazapine crystals)
 RN 61337-89-1 HCAPLUS
 CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

PI	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO-20000062782	A1	200001206	2000W0-US0010357	20000418 <-
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MG, MN, MT, MU, MY, NG, NK, NO, NZ, PL, PT, RO, SD, SE, SI, SV, SK, TR, TM, TM, TR, TZ, VN, ZA, ZW				
	RM: GH, GM, KE, LS, MW, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA-200400815	A1	20040106	2004CA-002366815	20000418 <-
	AU-2004004327	A1	20040102	2004AU-00094357	20000418 <-
	AU-781221	B2	20050512		
	TR-200103028	T2	200202121	2001TR-000003028	20000418 <-
	EP-1178605	A1	20020213	2000EP-000923457	20000418 <-
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	HU-2002000839	A3	20030528		
	JP-2004500324	I	20040108	2004JP-000611918	20000418 <-
	CN-1679586	A	20051012	2005CN-010004338	20000418 <-
	CN-1679587	A	20051012	2005CN-010004339	20000418 <-
	CN-1680365	A	20051012	2005CN-010004290	20000418 <-
	ZA-2001008220	A	20021208	2001ZA-000008220	20010105 <-
	IN-2001MN01253	A	20050819	2001IN-MN0001253	20011011 <-
	HR-200100747	A1	20021231	2001HR-00000747	20011015 <-
	US-2003000394	A1	20030908	2002US-000283093	20021030 <-
	US-6576764	B2	20020610		
	US-2003120068	A1	20030626	2003US-000348757	20030123 <-
	US-2004176591	A1	20040909	2004US-000800918	20040316 <-
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	2000US-00182745P	P	20000216		
	2000AU-000043577	A2	20000418		
	2000CN-000807574	A3	20000418		
	2000DE-000055695	A3	20000418		
	2000MO-US000357	W	20000818		
	2001US-000900646	A3	20010706		
	2001IN-MN0001253	A3	20011011		
	2002US-000283093	A3	20021030		
	2003US-000368441	B1	20030220		
OS	CASREACT 133:321900				
GI	MARPAT 133:321900				

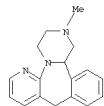


128 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound II [R3 = Ph, Me] followed by treating the resulting piperazine III with H2SO4. The mirtazapine intermediate 1-(3-cyano-4-methyl-2-phenyl-2-piperazinyl)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyano-4-methyl-2-phenylpiperazine with KOH at a temperature of at least about 130°C. The present invention also relates to new processes for reacting mirtazapine form crude mirtazapine.

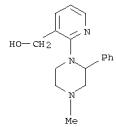
IT 85650-52-8 HCAPLUS
 RL: RAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); TBS-02001-03577
 (novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)

RN 85650-52-8 HCAPLUS
 CN Pyrazino[2,1-al]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

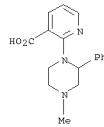


IT 61337-89-1P 61338-13-4P 303081-92-7P
 303081-92-7P 303081-92-7P
 RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)

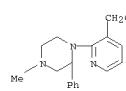
RN 61337-89-1 HCAPLUS
 CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



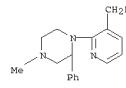
RN 61338-13-4 HCAPLUS
 CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



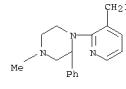
128 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
 RN 303081-92-7 HCAPLUS
 CN Piperazine, 1-[3-(chloromethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)



RN 303081-93-8 HCAPLUS
 CN Piperazine, 1-[3-(bromomethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)

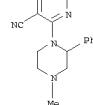


RN 303081-94-9 HCAPLUS
 CN Piperazine, 1-[3-(iodomethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)



IT 61337-88-0
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)

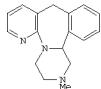
RN 61337-88-0 HCAPLUS
 CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

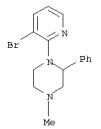
L28 ANSWER 12 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN
AN 1990:139001 HCPLUS

DN 112:139001
TI The synthesis of Org 3770 labeled with tritium, carbon-13 and carbon-14
AU Kortman, Frank M.; Van Rooij, Fons A. M.; Sperling, Eric G. M.;
Wieringa, Jop H.
CS Sci. Dev. Group, Organon Int. BV, Oss, 5340 BH, Neth.
SO Journal of Labelled Compounds and Radiopharmaceuticals (1989),
27(9), 1055-68
CQUS FLCRD4; ISSN: 0362-4803
DT Journal
LA English
OS CASREACT 112:139001
GI



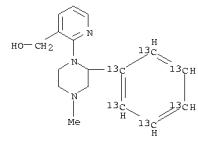
AB The syntheses of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770, I) labeled with ^3H (and ^2H), ^{13}C and ^{14}C are described. A piperazine derivative was synthesized and then under alkaline conditions with NaBH_4 or catalytic reductive dehalogenation of a chloro analog with 3H_2 , ^{13}C -labeled material was obtained in a 7-step synthesis starting from ^{13}C -labeled benzene, whereas I- ^{14}C was prepared in a 3-step synthesis starting with $^{14}\text{CO}_2$.

IT 125967-26-26
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and carboxylation of)
RN 125967-24-0 HCPLUS
CN Piperazine, 1-(3-bromo-2-pyridinyl)-4-methyl-2-phenyl- (CA INDEX NAME)

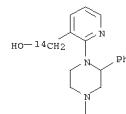


IT 125970-92-5P 125967-26-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclization of)
RN 125970-92-5 HCPLUS
CN 3-Pyridinemethanol, 2-[4-methyl-2-(phenyl- $^{13}\text{C}_6$)-1-piperazinyl]- (9CI) (CA INDEX NAME)

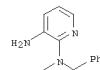
L28 ANSWER 12 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)



RN 125967-26-2 HCPLUS
CN 3-Pyridinemethanol- α -14C, 2-(4-methyl-2-phenyl-1-piperazinyl)- (9CI)
(CA INDEX NAME)



IT 125967-23-9B
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACTI (Reactant or reagent)
(preparation and diazotization-bromination of)
RN 125967-23-9 HCPLUS
CN 3-Pyridinamine, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



IT 125967-22-8B
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACTI (Reactant or reagent)
(preparation and hydrogenation of)
RN 125967-22-8 HCPLUS
CN Piperazine, 4-methyl-1-(3-nitro-2-pyridinyl)-2-phenyl- (CA INDEX NAME)

L28 ANSWER 12 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)

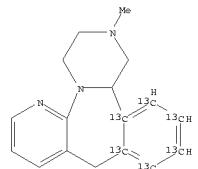
IT 125967-25-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)
RN 125967-25-1 HCPLUS
CN 3-Pyridinemcarboxylic-14C acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

IT 109133-29-1P 125970-93-6P 125967-27-3P
125967-28-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 109133-29-1 HCPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-t, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

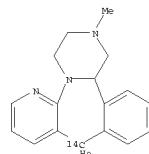
IT 125967-28-4 HCPLUS
125967-28-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 109133-29-1 HCPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-t, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

RN 125770-93-6 HCPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10a,11,12,13,14,14a-13C6, 1,2,3,4,10,14-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

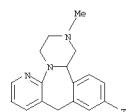
L28 ANSWER 12 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)



RN 125967-27-3 HCPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-14C, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 125967-28-4 HCPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-t, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN

AN 1977:29883 HCAPLUS

DN 86:29883

OREP 86:47874,47910

II Heterocyclic tetracyclic compounds

IN Van der Burg, Willem J.

PA AKZO N. V., Neth.

SG Ger. Offen., 40 pp.

COPEN: GWXXBX

DP Patents

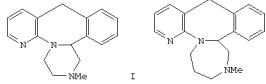
LA German

FAN.CNT 1

PATENT NO. KIND DATE APPLICATION NO. DATE

P1	DE-----2514406	A1	19761014	1976DE-002614406	19760402 <--
DE-----2514406	C2	19920230			
NU-----7504075	A	19761007	1975NL-000004075	19750405 <--	
NU-----189199	B	19920901			
NU-----189199	C	19930201			
ZK-----1499	A	19761330	1976ZA-000001786	19760323 <--	
AU-----7612261	A	19761007	1976AU-000012361	19760325 <--	
GB-----1543171	A	19790328	1976GB-000012270	19760326 <--	
CH-----622261	A5	19810331	1976CH-000003886	19760329 <--	
DK-----7601426	A	19761006	1976DK-000001426	19760330 <--	
DK-----142499	B	19801100			
DK-----142499	C	19801100			
FI-----62087	B	19820730	1976FI-000000884	19760401 <--	
FI-----62087	C	19821110			
BE-----840362	A1	19761004	1976BE-000165832	19760402 <--	
SE-----7513931	A	19761004	1976SE-000003931	19760402 <--	
SE-----420441	B	19820745			
SE-----420441	C	19820715			
JP-----5122099	A	19761025	1976JP-000037678	19760402 <--	
JP-----59042678	B	19841016			
FR-----2305986	A1	19761029	1976FR-000009686	19760402 <--	
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CA-----1076573	A1	19800429	1976CA-000249439	19760402 <--	
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HU-----179401	B	19821028			
PRAI 1975NL-000075040	A	19750405	<--		
1975NL-000004075		19750405	<--		

GI



AB The title compds., e.g. I and II, with nervous system-depressant and antihistaminic activities (no data), are prepared by various procedures. Thus, 2-(4-methyl-2-phenyl-1-piperazinyl)-3-pyridinecarboxylic nitrile which is hydrolyzed to the carboxylic acid and which is reduced to the hydroxylic acid derivative (III). Cyclization of 3.25 g III in concentrated H2SO4 at 20-35° gives after 2 hr and treatment with NaOH 2.43 g I.

IT 61337-89-1P

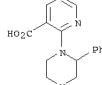
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(Preparation and cyclization of)

RN 61337-89-1 HCAPLUS

CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



IT 61337-69-7P 61337-70-0P 61337-71-2P

61337-72-2P 61337-73-3P 61337-74-4P

61337-75-5P 61337-86-8P 61337-87-9P

61364-36-1P 61364-37-2P 85650-52-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(Preparation and cyclization of)

RN 61337-69-7 HCAPLUS

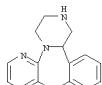
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-,

(2Z)-2-butenedioate (9CI) (CA INDEX NAME)

CM 1

CRN 61337-68-6

CMF C16 H17 N3

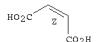


CM 2

CRN 110-16-7

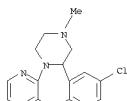
CMF C4 H4 O4

Double bond geometry as shown.



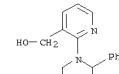
RN 61337-70-0 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 13-chloro-1,2,3,4,10,14b-hexahydro-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



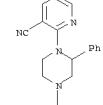
IT 61337-88-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(Preparation and hydrolysis of)

RN 61337-88-0 HCAPLUS

CN 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



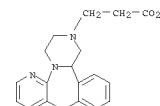
IT 61338-12-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(Preparation and pyrolysis of)

RN 61338-12-3 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-2(1H)-propanoic acid, 3,4,10,14b-tetrahydro- (CA INDEX NAME)



IT 61338-13-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(Preparation and reduction of)

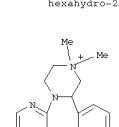
RN 61338-13-4 HCAPLUS

CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

IT 61337-71-1

RN 61337-71-1 HCAPLUS

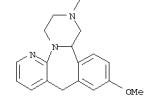
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepinium, 12-chloro-1,2,3,4,10,14b-hexahydro-2,2-dimethyl-, iodide (9CI) (CA INDEX NAME)



● I -

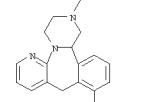
RN 61337-72-2 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-12-methoxy-2-methyl- (CA INDEX NAME)



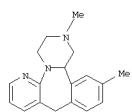
RN 61337-73-2 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2,11-dimethyl- (CA INDEX NAME)



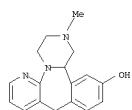
RN 61337-74-4 HCAPLUS

CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2,13-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

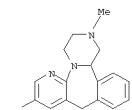


● HCl

RN 61337-79-5 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepin-13-ol, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

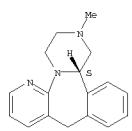


RN 61337-86-8 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 8-bromo-1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



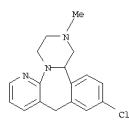
RN 61337-87-9 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 61364-36-1 HCPLUS

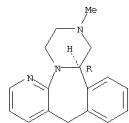
128 ANSWER 13 OF 13 HCPLUS COPYRIGHT 2008 ACS on STN (Continued)
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 12-chloro-1,2,3,4,10,14b-hexahydro-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



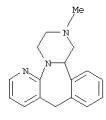
● 2 HCl

RN 61364-37-2 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 85650-52-8 HCPLUS
 CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



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(FILE 'HCAPLUS' ENTERED AT 18:14:44 ON 11 MAR 2008)
    DEL HIS Y

FILE 'HCAPLUS' ENTERED AT 19:20:44 ON 11 MAR 2008
L1      1 US20060229300/PN

FILE 'REGISTRY' ENTERED AT 19:20:51 ON 11 MAR 2008

FILE 'HCAPLUS' ENTERED AT 19:20:51 ON 11 MAR 2008
L2      TRA L1 1- RN :      3 TERMS

FILE 'REGISTRY' ENTERED AT 19:20:51 ON 11 MAR 2008
L3      3 SEA L2

FILE 'CASREACT' ENTERED AT 19:21:17 ON 11 MAR 2008
L4      STR
L5      STR L4
L6      STR L5
L7      0 L6
L8      13 L6 FULL
L9      8 L8 AND (PD<=20030710 OR AD<=20030710 OR PRD<=20030710)
L10     4 L8 AND PD<=20020710
L11     8 L9-10
L12     5 L8 NOT L11
        SEL AN 2 L11
L13     1 E291 AND L11
L14     7 L11 NOT L13

FILE 'REGISTRY' ENTERED AT 19:31:41 ON 11 MAR 2008
L15     STR L6
L16     0 L15
L17     34 L15 FULL
        SAV TEM J193C1REG/A L17

FILE 'CASREACT' ENTERED AT 19:33:06 ON 11 MAR 2008
        SAV TEM J193C1CASRE/A L8

FILE 'REGISTRY' ENTERED AT 19:33:13 ON 11 MAR 2008
L18     STR L6
L19     4 L18
L20     131 L18 FULL
        SAV TEM J193C1REG2/A L20

FILE 'HCAPLUS' ENTERED AT 19:34:04 ON 11 MAR 2008
L21     33 L17
L22     836 L20
L23     23 L21 (L) RACT+NT/RL
L24     56 L22 (L) (PREP+NT OR FORM+NT) /RL
L25     22 L23 AND L24
L26     1 L25 AND L1
L27     21 L25 NOT L26
L28     13 L27 AND (PD<=20030710 OR AD<=20030710 OR PRD<=20030710)
L29     8 L27 NOT L28

FILE 'HCAOLD' ENTERED AT 19:38:23 ON 11 MAR 2008
L30     0 L17 AND L20

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